5.11 FLONICAMID (282)

TOXICOLOGY

Flonicamid is the ISO-approved common name for *N*-cyanomethyl-4-(trifluoromethyl)nicotinamide (IUPAC), with CAS number 158062-67-0. It is a novel systemic pyridine carboxamide insecticide with selective activity against hemipterous pests, such as aphids and whiteflies, and thysanopterous pests.

Flonicamid has not previously been evaluated by JMPR and was reviewed by the present Meeting at the request of CCPR.

All critical studies contained statements of compliance with GLP.

Biochemical aspects

In metabolism studies conducted in rats using flonicamid labelled with ^{14}C at the 3-nicotinamide position, flonicamid was rapidly absorbed. T_{max} values were under 1 hour at the low and high doses (2 and 400 mg/kg bw, respectively), and half-lives were between 4.5 hours at the low dose and 11.6 hours at the high dose. Radiolabel concentrations in the plasma in all dose groups decreased in a manner consistent with first-order kinetics. The majority of administered radioactivity was excreted in the urine within the first 24 hours. There was no evidence of bioaccumulation following repeated dosing. Distribution to the tissues was extensive, with levels similar to concentrations in plasma; however, slightly higher concentrations were seen in the liver, kidneys, adrenals, thyroid and ovaries following single or repeated dosing in both sexes and in the lungs following repeated dosing in males.

The main urinary residue was unchanged parent, followed by 4-trifluoromethylnicotinamide (TFNA-AM), which was also the predominant metabolite in the faeces and bile. Other metabolites were 4-trifluoromethylnicotinic acid (TFNA), TFNA-AM *N*-oxide conjugate (not specified), *N*-(4-trifluoromethylnicotinoyl) glycinamide (TFNG-AM), *N*-(4-trifluoromethylnicotinoyl) glycine (TFNG) and TFNA-AM.

Toxicological data

In rats, flonicamid is of moderate acute oral toxicity (LD_{50} = 884 mg/kg bw), low acute dermal toxicity (LD_{50} > 5000 mg/kg bw) and low acute inhalation toxicity (LC_{50} > 4.90 mg/L). Flonicamid was slightly irritating to the eyes and non-irritating to the skin of rabbits. It was not a dermal sensitizer in guinea-pigs.

The main target organs are the liver, haematopoietic system and lungs in mice and the liver and kidneys in rats. In long-term studies in rats, the skeletal muscles, eyes and stomach are also targets. In dogs, effects on general condition and clinical signs are the main signs of toxicity.

In a 90-day range-finding study in mice, which tested dietary flonicamid concentrations of 0, 100, 1000 and 7000 ppm (equal to 0, 15, 154 and 1069 mg/kg bw per day for males and 0, 20, 192 and 1248 mg/kg bw per day for females, respectively), increased incidences of minimal centrilobular hypertrophy in the liver in males and increased incidences of minimal to moderately severe extramedullary haematopoiesis in the spleen were seen in both sexes at 1000 ppm (equal to 154 mg/kg bw per day). The lungs were not evaluated in this study.

In a 28-day range-finding study in rats, dietary flonicamid concentrations of 0, 50, 100, 500, 1000 and 5000 ppm (equal to 0, 3.61, 7.47, 36.45, 73.8 and 353.4 mg/kg bw per day, respectively) for males and 0, 100, 500, 1000, 5000 and 10 000 ppm (equal to 0, 7.47, 36.45, 73.8, 353.4 and 642 mg/kg bw per day, respectively) for females were tested. The kidneys of two males per dose at 0 and 5000 ppm were immunostained for α_2u-globulin. In addition to effects on clinical chemistry and haematology parameters and on the liver (e.g. dark coloration, hepatocellular hypertrophy and increased incidence of liver enlargement) at 5000 ppm in males and females, males also exhibited increased incidence of pale kidneys, increased kidney weights, increased incidence of hyaline droplet depositions of proximal tubular cells and granular casts of the kidneys. Hyaline droplets were positive

for α_2u-globulin. As a result, the Meeting considered hyaline droplets of the kidneys to be specific to male rats and not applicable to the human risk assessment.

In a 90-day study in the rat, which tested dietary flonicamid concentrations of 0, 50, 200, 1000 and 2000 ppm (equal to 0, 3.08, 12.11, 60.0 and 119.4 mg/kg bw per day, respectively) for males and 0, 200, 1000 and 5000 ppm (equal to 0, 14.52, 72.3 and 340.1 mg/kg bw per day, respectively) for females, the NOAEL was 200 ppm (equal to 12.11 mg/kg bw per day), based on increased kidney weights, granular casts and increased basophilic changes in the renal tubules in males at 1000 ppm (equal to 60 mg/kg bw per day). The Meeting was unable to dismiss the possible human relevance of the kidney findings in the male rats because of the observation of kidney effects in female rats at higher doses in this study and in female dogs (see below).

In a 90-day study in dogs, which tested capsule flonicamid doses of 0, 3, 8, 20 and 50 (females only) mg/kg bw per day, the NOAEL was 8 mg/kg bw per day, based on vomiting, ataxia, decreased activity, laboured breathing, prostration, decreased body weight and body weight gain in both sexes, decreased feed consumption in females and decreased thymus weight in males at 20 mg/kg bw per day. Tubular vacuolation of the inner cortex of the kidney was noted in 2/4 females at 50 mg/kg bw per day.

In a 1-year study in dogs, which tested capsule flonicamid doses of 0, 3, 8 and 20 mg/kg bw per day, the NOAEL was 8 mg/kg bw per day, based on vomiting and increased reticulocytes in males and females and decreased body weight gain in females at 20 mg/kg bw per day.

The Meeting concluded that the overall NOAEL for oral toxicity in dogs was 8 mg/kg bw per day, and the overall LOAEL was 20 mg/kg bw per day.

In an 18-month study in CD-1 mice, which tested dietary flonicamid concentrations of 0, 250, 750 and 2250 ppm (equal to 0, 29, 88 and 261 mg/kg bw per day for males and 0, 38, 112 and 334 mg/kg bw per day for females, respectively), a NOAEL was not identified, as an increase in the combined incidence of alveolar/bronchiolar adenomas and/or carcinomas in both sexes, an increase in extramedullary haematopoiesis of the spleen, increased pigment deposition in the femoral and sternal bone marrow, increased centrilobular hepatocellular hypertrophy, increased incidence of hyperplasia/hypertrophy of the epithelial cells of the terminal bronchioles and masses/nodules in lung of males and decreased cellularity of the femoral bone marrow in females were observed at 250 ppm (equal to 29 mg/kg bw per day), the lowest dose tested.

In a second 18-month study in CD-1 mice, which tested dietary flonicamid concentrations of 0, 10, 25, 80 and 250 ppm (equal to 0, 1.2, 3.1, 10.0 and 30.3 mg/kg bw per day for males and 0, 1.4, 3.7, 11.8 and 36.3 mg/kg bw per day for females, respectively), the NOAEL was 80 ppm (equal to 10.0 mg/kg bw per day), based on an increase in lung adenomas in males, a slight lung hyperplasia/hypertrophy in the terminal bronchiole epithelial cells in males and females and an increased incidence of hyperplasia of alveolar epithelial cells in females at 250 ppm (equal to 30.3 mg/kg bw per day).

The overall NOAEL for the two long-term mouse studies was 80 ppm (equal to 10.0 mg/kg bw per day), and the overall LOAEL was 250 ppm (equal to 29 mg/kg bw per day).

In a 2-year study in rats, which tested dietary flonicamid concentrations of 0, 50, 100, 200 and 1000 ppm (equal to 0, 1.84, 3.68, 7.32 and 36.5 mg/kg bw per day, respectively) for males and 0, 200, 1000 and 5000 ppm (equal to 0, 8.92, 44.1 and 219 mg/kg bw per day, respectively) for females, the NOAEL was 200 ppm (equal to 7.32 mg/kg bw per day), based on decreased body weight and body weight gain, decreased rearing, and increased incidences of keratitis and pelvic dilatation in the kidneys in males and decreased triglyceride levels and increased striated muscle atrophy in females at 1000 ppm (equal to 36.5 mg/kg bw per day). No treatment-related tumours were observed in this study.

The Meeting concluded that flonicamid causes lung tumours in CD-1 mice, but is not carcinogenic in rats.

Flonicamid was tested for genotoxicity in an adequate range of assays, both in vitro and in vivo. No evidence of genotoxicity was found.

The Meeting concluded that flonicamid is unlikely to be genotoxic.

Mechanistic studies were performed in support of the hypothesis that lung tumours caused by flonicamid were due to a non-genotoxic proliferative process specific to the Clara cells of CD-1 mice. The investigators identified a possible threshold for mitogenic effects between 80 and 250 ppm (equal to 12.3 and 40.9 mg/kg bw per day, respectively) in a 3-day dietary toxicity study in male mice. Flonicamid caused a transient increase in elongation and hyperplasia/hypertrophy of the Clara cells in the lungs of male mice. In a short-term dietary study of flonicamid and its metabolites in CD-1 mice, proliferation of the respiratory bronchiolar epithelial cells was specific to the parent compound, as male mice exposed to TFNG, TFNA and TFNA-AM did not exhibit this finding. Flonicamid did not cause such proliferation in female rats or in B6C3F1 and C57 mice. Overall, the mechanistic studies support the plausibility of the proposed mode of action.

In view of the lack of genotoxicity, the absence of carcinogenicity in rats and the fact that lung tumours were observed only in CD-1 mice with a plausible mode of action, the Meeting concluded that flonicamid is unlikely to pose a carcinogenic risk to humans from the diet.

In a reproductive toxicity study in rats, which tested dietary concentrations of 0, 50, 300 and 1800 ppm (equal to 0, 3.7, 22.3 and 133 mg/kg bw per day for males and 0, 4.4, 26.5 and 153 mg/kg bw per day for females, respectively), the NOAEL for parental toxicity was 300 ppm (equal to 22.3 mg/kg bw per day), based on increased proximal tubule cell vacuolation of the kidney observed in females and increased kidney weights, tubular basophilic change and granular casts observed in males at 1800 ppm (equal to 133 mg/kg bw per day). The NOAEL for offspring toxicity was 300 ppm (equal to 26.5 mg/kg bw per day), based on delayed sexual maturation and decreased uterine weight in F_1 females at 1800 ppm (equal to 153 mg/kg bw per day). The NOAEL for reproductive toxicity was 1800 ppm (equal to 133 mg/kg bw per day), the highest dose tested. Minor changes in levels of reproductive hormones observed at 300 ppm and above in the absence of any adverse effects on reproduction were not considered toxicologically relevant.

In a range-finding developmental toxicity study in rats, which tested gavage flonicamid doses of 0, 30, 100, 300 and 1000 mg/kg bw per day, the first signs of toxicity in the dams were clinical signs of eye discharge, forelimb wounding, loss of abdominal fur, soiled fur around the external genital region, vaginal haemorrhage, white discharge on the tray, and decreased body weight gain and feed consumption at 1000 mg/kg bw per day. There were no external abnormalities at the highest dose tested.

In a developmental toxicity study in rats, which tested gavage flonicamid doses of 0, 20, 100 and 500 mg/kg bw per day, the NOAEL for maternal toxicity was 100 mg/kg bw per day, based on increased liver weights and histopathological changes in the liver and kidneys observed at 500 mg/kg bw per day. The NOAEL for embryo and fetal toxicity was 100 mg/kg bw per day, based on an increase in cervical rib skeletal variations observed at 500 mg/kg bw per day.

In a range-finding developmental toxicity study in rabbits, which tested gavage flonicamid doses of 0, 3, 10 and 30 mg/kg bw per day, decreased body weight gain, feed consumption and gravid uterine weight were observed in the dams at 30 mg/kg bw per day. In the offspring, a decreased number of live fetuses, decreased fetal weights and decreased percentage of male fetuses were observed at 30 mg/kg bw per day.

In a developmental toxicity study in rabbits, which tested gavage flonicamid doses of 0, 2.5, 7.5 and 25 mg/kg bw per day, the NOAEL for maternal toxicity was 7.5 mg/kg bw per day, with decreased body weight, feed consumption and gravid uterine weight being observed at 25 mg/kg bw per day. The NOAEL for embryo and fetal toxicity was 7.5 mg/kg bw per day, with decreased fetal weights being observed at 25 mg/kg bw per day.

In an acute neurotoxicity study in rats, which tested flonicamid at gavage doses of 0, 100, 300, 600 (males only) and 1000 (females only) mg/kg bw per day, signs of systemic toxicity,

decreased total locomotor activity, increased resting time and increased landing foot splay were observed at the high dose in both sexes, and increased forelimb grip strength was observed in females at the high dose. The effects were not considered specific to neurotoxicity, but rather indicative of systemic toxicity.

In a 13-week neurotoxicity study in rats, which tested dietary concentrations of 0, 200, 1000 and 10 000 ppm (equal to 0, 13, 67 and 625 mg/kg bw per day for males and 0, 16, 81 and 722 mg/kg bw per day for females, respectively), effects at the high dose included decreased body weight gain and feed consumption in males and females, decreased body weights in females, decreased rearing and total motor activity in males, decreased locomotor activity in males and females, and increased landing foot splay in males. The effects were not considered specific to neurotoxicity, but rather indicative of systemic toxicity.

The Meeting concluded that flonicamid is not neurotoxic.

In a 28-day immunotoxicity study in female mice, which tested dietary flonicamid concentrations of 0, 100, 600 and 6000 ppm (equal to 0, 23.2, 142 and 1540 mg/kg bw per day, respectively), clinical signs of toxicity and decreased body weight and body weight gain were observed at the high dose. No specific immunotoxic effects were observed.

The Meeting concluded that flonicamid is not immunotoxic.

Toxicological data on metabolites and/or degradates

Acute toxicity and genotoxicity studies were performed on five metabolites: TFNA (plants, also in rat), TFNA-AM (all livestock commodities, also in rat), TFNG (plants, also in rat), TFNG-AM (rat) and 6-hydroxy-4-trifluoromethylnicotinic acid (TFNA-OH) (secondary crops). Additionally, short-term dietary studies were conducted with TFNA and TFNG.

TFNA was of low acute oral toxicity (LD_{50} > 2000 mg/kg bw) and did not show evidence of genotoxicity in an Ames test. In a 90-day toxicity study in rats, TFNA was given at a dietary concentration of 0, 50 or 2000 ppm for males (equal to 0, 3.42 and 136 mg/kg bw per day, respectively) and 0, 200 or 5000 ppm for females (equal to 0, 15.9 and 409 mg/kg bw per day, respectively). The modest increase in blood glucose levels in females at 5000 ppm was not considered toxicologically significant, and no other changes were observed. The NOAEL was 2000 ppm (equal to 136 mg/kg bw per day) for males and 5000 ppm (equal to 409 mg/kg bw per day) for females, the highest doses tested. The Meeting concluded that TFNA is markedly less toxic than the parent compound.

TFNA-AM was of low acute oral toxicity (LD_{50} > 2000 mg/kg bw) and did not show evidence of genotoxicity in an Ames test. As TFNA-AM is a major rat metabolite, the Meeting concluded that TFNA-AM would be no more toxic than the parent compound.

TFNG, a minor metabolite found in the rat liver, but a major plant metabolite, was of low acute oral toxicity (LD_{50} > 2000 mg/kg bw) and did not show evidence of genotoxicity in an Ames test. In a 90-day toxicity study in rats, TFNG was given at a dietary concentration of 0, 50 or 2000 ppm for males (equal to 0, 3.56 and 135 mg/kg bw per day, respectively) and 0, 200 or 5000 ppm for females (equal to 0, 16.5 and 411 mg/kg bw per day, respectively). The NOAEL was 2000 ppm (equal to 135 mg/kg bw per day) for males and 5000 ppm (equal to 411 mg/kg bw per day) for females, the highest doses tested. The Meeting concluded that TFNG is markedly less potent than the parent compound.

TFNA-OH was of low acute oral toxicity (LD_{50} > 2000 mg/kg bw) and did not show evidence of genotoxicity in an Ames test. The Meeting concluded that TFNA-OH would likely be less potent than the parent compound, taking into consideration the limited data available and the structural similarity to TFNA.

TFNG-AM was of low acute oral toxicity (LD_{50} > 2000 mg/kg bw) and did not show evidence of genotoxicity in an Ames test. The Meeting concluded that TFNG-AM would be no more toxic than the parent compound.

Human data

No information was provided on the health of workers involved in the manufacture or use of flonicamid.

The Meeting concluded that the existing database on flonicamid was adequate to characterize the potential hazards to the general population, including fetuses, infants and children.

Toxicological evaluation

The Meeting established an ADI of 0–0.07 mg/kg bw on the basis of a NOAEL of 7.32 mg/kg bw per day in the 2-year rat study, based on decreased body weight, decreased rearing, effects on clinical chemistry and effects on kidney and muscle observed at 36.5 mg/kg bw per day. This ADI is supported by the overall NOAEL of 8 mg/kg bw per day in dogs and the NOAELs of 7.5 mg/kg bw per day for maternal and embryo/fetal toxicity in the developmental toxicity study in rabbits. A safety factor of 100 was applied. The margin between the upper bound of the ADI and the LOAEL of 30.3 mg/kg bw per day for lung adenomas in male mice is about 430.

The Meeting concluded that the ADI would apply to the sum of flonicamid and the metabolites TFNA-AM and TFNG-AM, expressed as flonicamid.

The Meeting concluded that it was not necessary to establish an ARfD for flonicamid in view of its low acute toxicity and the absence of developmental toxicity and any other toxicological effects that would be likely to be elicited by a single dose.

Levels relevant to risk assessment of flonicamid

Species	Study	Effect	NOAEL	LOAEL
Mouse	Eighteen-month studies of toxicity and carcinogenicity[a,b]	Toxicity	80 ppm, equal to 10.0 mg/kg bw per day	250 ppm, equal to 29 mg/kg bw per day
		Carcinogenicity	80 ppm, equal to 10.0 mg/kg bw per day	250 ppm, equal to 29 mg/kg bw per day
Rat	Two-year study of toxicity and carcinogenicity[a]	Toxicity	200 ppm, equal to 7.32 mg/kg bw per day	1 000 ppm, equal to 36.5 mg/kg bw per day
		Carcinogenicity	1 000 ppm, equal to 36.5 mg/kg bw per day[c]	–
	Two-generation study of reproductive toxicity[a]	Reproductive toxicity	1 800 ppm, equal to 133 mg/kg bw per day[c]	–
		Parental toxicity	300 ppm, equal to 22.3 mg/kg bw per day	1 800 ppm, equal to 133 mg/kg bw per day
		Offspring toxicity	300 ppm, equal to 26.5 mg/kg bw per day	1 800 ppm, equal to 153 mg/kg bw per day
	Developmental toxicity study[d]	Maternal toxicity	100 mg/kg bw per day	500 mg/kg bw per day
		Embryo and fetal toxicity	100 mg/kg bw per day	500 mg/kg bw per day
	Acute neurotoxicity study[d]	Neurotoxicity	600 mg/kg bw per day[c]	–

Species	Study	Effect	NOAEL	LOAEL
	Subchronic neurotoxicity study[a]	Neurotoxicity	625 mg/kg bw per day[c]	–
Rabbit	Developmental toxicity study[d]	Maternal toxicity	7.5 mg/kg bw per day	25 mg/kg bw per day
		Embryo and fetal toxicity	7.5 mg/kg bw per day	25 mg/kg bw per day
Dog	Thirteen-week and 1-year studies of toxicity[b,e]	Toxicity	8 mg/kg bw per day	20 mg/kg bw per day

[a] Dietary administration.
[b] Two or more studies combined.
[c] Highest dose tested.
[d] Gavage administration.
[e] Capsule administration.

Estimate of acceptable daily intake (ADI) (for sum of flonicamid and metabolites TFNA-AM and TFNG-AM, expressed as flonicamid)

0–0.07 mg/kg bw

Estimate of acute reference dose (ARfD)

Unnecessary

Information that would be useful for the continued evaluation of the compound

Results from epidemiological, occupational health and other such observational studies of human exposure

Critical end-points for setting guidance values for exposure to flonicamid

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Rapid, almost complete at low and high doses
Dermal absorption	Not given
Distribution	Widely distributed at levels similar to plasma, higher concentrations in liver, kidneys, adrenals, thyroid and ovaries and in lungs in males following repeated dosing
Potential for accumulation	No evidence of accumulation
Rate and extent of excretion	93–98% excreted within 7 days; predominantly in urine within the first 24 h
Metabolism in animals	Multiple metabolites, approximately 50% excreted unchanged
Toxicologically significant compounds in animals and plants	Flonicamid, TFNA-AM, TFNG-AM
Acute toxicity	
Rat, LD_{50}, oral	884 mg/kg bw
Rat, LD_{50}, dermal	> 5 000 mg/kg bw
Rat, LC_{50}, inhalation	> 4.90 mg/L
Rabbit, dermal irritation	Not irritating
Rabbit, ocular irritation	Slightly irritating

Guinea-pig, dermal sensitization	Not sensitizing (Magnusson and Kligman maximization test or Buehler method)
Short-term studies of toxicity	
Target/critical effect	Clinical signs of toxicity and decreased body weight (dog)
Lowest relevant oral NOAEL	8 mg/kg bw per day (dog)
Lowest relevant dermal NOAEL	1 000 mg/kg bw per day (rat)
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Decreased body weight, decreased rearing, effects on clinical chemistry, effects on kidney and muscle
Lowest relevant NOAEL	7.32 mg/kg bw per day (rat)
Carcinogenicity	Carcinogenic in mice, but not in rats[a]
Genotoxicity	
	Not genotoxic[a]
Reproductive toxicity	
Target/critical effect	Kidney effects in parents; delayed sexual maturation and decreased uterine weight in female offspring
Lowest relevant parental NOAEL	22.3 mg/kg bw per day (rat)
Lowest relevant offspring NOAEL	26.5 mg/kg bw per day (rat)
Lowest relevant reproductive NOAEL	133 mg/kg bw per day (highest dose tested; rat)
Developmental toxicity	
Target/critical effect	Decreased maternal body weight, gravid uterine weight and fetal weight
Lowest relevant maternal NOAEL	7.5 mg/kg bw per day (rabbit)
Lowest relevant embryo/fetal NOAEL	7.5 mg/kg bw per day (rabbit)
Neurotoxicity	
Acute neurotoxicity NOAEL	600 mg/kg bw (highest dose tested; rat)
Subchronic neurotoxicity NOAEL	625 mg/kg bw per day (highest dose tested; rat)
Developmental neurotoxicity NOAEL	No data
Other toxicological studies	
Immunotoxicity NOAEL	1540 mg/kg bw per day (highest dose tested; mouse)
Studies on toxicologically relevant metabolites	TFNA-AM Oral LD_{50} > 2 000 mg/kg bw (rat) No evidence of genotoxicity TFNG-AM Oral LD_{50} > 2 000 mg/kg bw (rat) No evidence of genotoxicity
Mechanistic/mode of action studies	Causes increased cell division in CD-1 mouse lungs after 3 d at a threshold between 12.3 and 40.9 mg/kg bw per day Does not cause similar increases in rats, B6C3F1 or C57 mice TFNG, TFNA and TFNA-AM do not cause an increase in cell division Following a recovery period of 1–3 weeks, there is no evidence of increased cell division

Medical data	
	No information was provided

[a] Unlikely to pose a carcinogenic risk to humans from the diet.

Summary

	Value	Study	Safety factor
ADI	0–0.07 mg/kg bw	Two-year toxicity study (rat)	100
ARfD	Unnecessary	–	–

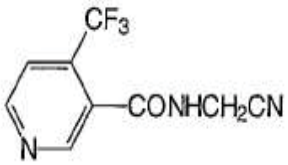
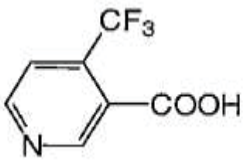
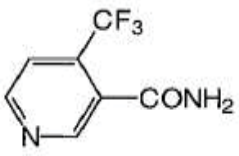
RESIDUE AND ANALYTICAL ASPECTS

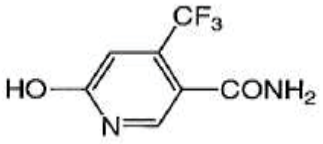
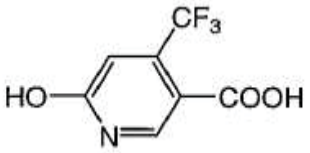
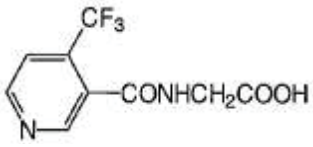
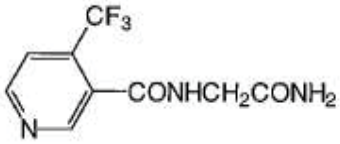
Flonicamid is a new insecticide for control of aphids and other sucking insects. It belongs to a new class of chemistry known as pyridinecarboxamide. At the Forty-sixth Session of the CCPR, flonicamid was scheduled for evaluation, for both toxicology and residues, as a new compound by the 2015 JMPR.

The Meeting received information on the metabolism of flonicamid in peaches, bell peppers, potatoes, wheat, lactating goats, laying hens and rotational crops, environmental fate, methods of residue analysis, freezer storage stability, GAP, supervised residue trials on various fruits, vegetables, tree nuts, oil seeds, dried hops, mint and tea, processing studies as well as livestock feeding studies.

In this document, the code names and chemical structures of the metabolites were as follows:

Flonicamid is *N*-cyanomethyl-4-(trifluoromethyl)nicotinamide (IUPAC).

Code Name	*Structure*	*Chemical Name*
Flonicamid IKI-220		*N*-cyanomethyl-4-(trifluoromethyl)nicotinamide
TFNA		4-trifluoromethylnicotinic acid
TFNA-AM		4-trifluoromethylnicotinamide

OH-TFNA-AM		6-hydroxy-4-trifluoromethylnicotinamide
TFNA-OH		6-hydroxy-4-trifluoromethylnicotinic acid
TFNG		*N*-(4-trifluoromethylnicotinoyl)glycine
TFNG-AM		*N*-(4-trifluoromethylnicotinoyl)glycinamide

Environmental fate in soil

The FAO Manual (FAO, 2009) explains the data requirements for studies of environmental fate. The focus should be on those aspects that are most relevant to MRL setting. For flonicamid, supervised residue trials were received for foliar spray on permanent crops and on annual crops. Therefore, according to the FAO manual, only studies on aerobic degradation, photolysis and rotational crops (confined, field) were evaluated.

Degradation

The route of degradation of [^{14}C]flonicamid in soil under aerobic conditions was investigated in a biologically active loamy sand soil collected from Madison, Ohio, USA and stored in a greenhouse. Flonicamid rapidly declined from 99.3% of the applied radioactivity (AR) at Day 0 to 2.3% by Day 30, resulting in a DT_{50} of 1 day and a DT_{90} of 3.4 days. TFNA and TFNA-OH were major components of the residue with TFNG, TFNG-AM and TFNA-AM all identified as minor metabolites.

The rate of aerobic degradation of [^{14}C]flonicamid, radiolabelled at the 3 position of the pyridine was investigated in three biologically active soils (sandy loam and sand at 10 °C and/or 20 °C)

For the soils incubated at 20 °C the DT_{50} and DT_{90} values for flonicamid ranged from 0.7 to 1.8 days and 2.3 to 6.0 days, respectively. For the soil incubated at 10 °C, the DT_{50} and DT_{90} values for flonicamid were 2.4 days and 7.9 days, respectively. TFNA, TFNA-OH and TFNG-AM were the major degradates in all soils over the course of the study. Minor degradates TFNG and TFNA-AM were detected at all sampling points over the course of the study. All of the degradates were metabolised and mineralised to carbon dioxide and immobilised as soil-bound residue.

Photolysis

The photochemical degradation of [pyridyl-^{14}C]flonicamid was investigated in a loamy sand under laboratory conditions.

[^{14}C]Flonicamid decreased to 60% of the applied radioactivity (AR) after 15 days of continuous illumination, resulting in a DT_{50} of 22 days. Concurrently, the major metabolite TFNG-AM was detected in Day 1 sample extracts and increased by Day 15. TFNA-AM and TFNG were also detected as minor metabolites in the illuminated soils, reaching maximum concentrations of 5% AR (Day 11 and Day 15) and 2% AR (Day 15), respectively.

In summary, based on the results of the environmental fate studies, flonicamid as well as its metabolites are likely to readily degrade and not persist in aerobic soil environments.

Plant metabolism

The metabolism of flonicamid was studied in peaches, bell peppers, potatoes and wheat.

Peach

Flonicamid, radiolabelled at the 3 position of the pyridine ring and formulated as a wettable granule, was applied twice to peach trees grown outdoor, with a 14-day re-treatment interval, at rates of 100 g ai/ha (low rate) or 500 g ai/ha (high rate) per application. Mature fruits and leaves were harvested 21 days after the last treatment (DALA). Overall total radioactive residues (TRRs) in fruits at the low rate and the high rate were 0.10 mg eq/kg and 0.32 mg eq/kg, respectively, while in the leaves, TRRs followed the same trend, where residues were lower at the lower application rate (6.2 mg eq/kg) compared to those at the higher treatment rate (24 mg eq/kg).

The peaches were subjected to a surface wash using deionised water which removed very little radioactivity (≤ 15% TRRs), evidence of limited penetration. The majority of the TRRs were partitioned into the juice fraction (64–73% of the TRR) and to a lesser extent into the pulp (21% TRRs). While juice was not further extracted with organic solvents, extraction of the pulp with acetonitrile:water:phosphoric acid recovered 92% TRR. At both treatment rates, flonicamid (30–60% TRRs) and TFNA (17–49% TRRs) were the predominant residues in juice and pulp. All other metabolites, TFNG, TFNG-AM and TFNA- AM were ≤ 6% TRRs.

Bell pepper

A single application of flonicamid, radiolabelled at the 3 position of the pyridine ring, formulated as a 50% wettable granule formulation, was made to greenhouse grown bell pepper plants at 100 g ai/ha. Fruits and leaves were harvested 7 days and 14 days after treatment (DAT).

The TRRs in fruits decreased insignificantly from 0.17 mg eq/kg (7 DAT) to 0.11 mg eq/kg (14 DAT) while TRRs in leaves decreased from 2.2 mg eq/kg, when harvested 7 days after treatment to 1.4 mg eq/kg at 14 DAT.

The %TRR in the methanol:water surface wash for both leaves and fruits decreased as the corresponding extracted TRRs (61–81% TRRs) and those in the post-extraction solids (PES) increased with increasing DAT. This trend demonstrated the penetration of the radioactivity from the surface into the leaves and fruits.

Flonicamid and TFNG were the predominant residues in leaves (47–74% TRRs and 12–28% TRRs, respectively) while only flonicamid was the predominant residue in fruits (77–91% TRRs) at both harvest intervals. All identified metabolites (TFNA, TFNA-AM and TFNG-AM) were either not detected or were ≤ 12% TRRs.

Potato

Potato plants maintained outdoor were treated, either at the lower rate of 100 g ai/ha or the higher rate of 500 g ai/ha, with flonicamid radiolabelled at the 3 position of the pyridine ring and formulated as a 50% wettable powder. Both treatments were repeated at a two-week interval and potato tubers and foliage were harvested 14 days after the last application.

Overall TRRs in tubers at the low rate and the high rate were 0.11 mg eq/kg and 0.20 mg eq/kg, respectively, while those in mature foliage were higher than those in tubers;

1.5 mg eq/kg at the low rate and 7.7 mg eq/kg at the high rate. Considering the applications were made to the foliage of the potato plants, the presence of measurable TRRs in the tubers is evidence of translocation of the radioactivity from the foliage to the tubers. Furthermore, while the TRRs in tubers and foliage increased with increased application, the distribution of TRRs was relatively the same irrespective of the treatment rate.

Extraction of the potato tubers with ACN and ACN:water recovered up to 93% TRRs while extraction of potato foliage with ACN:water:acetic acid recovered up to 90% TRRs. Analysis of each of the extracted fractions of potato tubers and foliage from the low and high rate demonstrated that the major components of the residue, TFNA and TFNG, accounted for a significant portion of the TRRs. Moreover, TFNA accounted for 34% TRRs in tubers and 12–17% TRRs in foliage at both rates while TFNG accounted for 25–39% TRRs in tubers and 28–36% TRRs in leaves at both rates. The parent, flonicamid, accounted for 6–19% TRRs in potato tubers and 10–25% TRRs in foliage. Each of the other identified metabolites (TFNA conjugate, TFNG-AM, TFNA-AM, PM-1a, PM-1b and PM-3a) accounted for < 10% TRRs in tubers and in foliage. Overall, the general metabolic profile in foliage was similar to that in tubers.

Spring wheat

Spring wheat plants grown outdoor were treated with flonicamid, radiolabelled at the 3 position of the pyridine ring and formulated as a wettable powder, at a single application rate of 100 g ai/ha or 2 applications at 100 g ai/ha with a re-treatment interval of 7 days. Forage and hay were harvested 14 days and 42 days, respectively, after the single application. Approximately 95 days after the second treatment (200 g ai/ha/season), mature plants were harvested and separated into straw, chaff and grain.

Overall residues were lower in the wheat grain sample (2.6 mg eq/kg) than the straw (5.6 mg eq/kg) or chaff (6.6 mg eq/kg). The TRRs in the chaff were higher compared to straw potentially because of tissue size differences (higher surface area to weight ratio) assuming a uniform application. Further to this, considering the timing of application of the test material and the measurable TRRs in grain, chaff and straw at maturity, there appears to have been translocation of the radioactivity from the site of application to the mature plant parts.

Only forage and hay were analysed to elucidate the nature of the flonicamid residues. Extraction of these matrices with ACN:water:acetic acid recovered 96% TRRs. The analysis of forage and hay samples demonstrated that the nature and distribution of metabolites were similar in both matrices. The parent compound, flonicamid, and the TFNG metabolite represented the majority of the TRRs in both the forage (flonicamid: 43% TRRs; TFNG: 33% TRRs) and hay (flonicamid: 22%TRRs; TFNG: 53% TRRs). Metabolites TFNG-AM, TFNA and TFNA-AM were present at ≤ 13% TRRs.

In a second spring wheat metabolism study, plants grown outdoor were treated with flonicamid, radiolabelled at the 3 position of the pyridine ring and formulated as a wettable granule, at rates equivalent to 100 g ai/ha or 500 g ai/ha. The wheat plants were harvested 21 DAT and separated into straw (leaves and stem), chaff and grain (with hulls attached).

The TRRs in wheat straw, chaff and grain increased with increased application rate with the highest TRRs observed in chaff, followed by straw and grain, irrespective of the application rate. The distribution of TRRs was relatively the same irrespective of the treatment rate.

Similar to the first wheat metabolism study, extraction with ACN:water:acetic acid recovered 80–94%TRRs with flonicamid (24–50%TRRs) and TFNG (17–44% TRRs) representing the predominant residues at both treatment rates. All identified metabolites (TFNA, TFNG-AM, TFNA-AM and N-oxide TFNA AM) were either not detected or were each ≤ 10% TRR.

In summary, the Meeting determined that the degree of metabolism in all crops tested, following foliar application, was qualitatively similar, with the parent compound as the predominant residue. The major metabolic pathway of flonicamid in plants involved hydrolysis of the cyano group and the amide groups.

Rotational crops

In the confined rotational crop study, flonicamid, radiolabelled at the 3 position of the pyridine ring and formulated as a wettable granule was applied twice to loamy sand soil at a rate equivalent to 100 g ai/ha at an interval of two weeks. After the appropriate plant-back intervals (PBIs) of 30, 120 or 360 days, the rotational crops, representative of the root vegetable (carrot), small grain (wheat), and leafy vegetable (lettuce) crop groups, were planted.

TRRs in all raw agricultural commodities (RACs) declined with prolonged PBIs such that, at the 120-day PBI, no further characterization/identification of the TRRs was performed for immature and mature lettuce and mature carrot roots due to the low total radioactivity. Further to this, at the 360-day PBI, none of the TRRs from any of the crop parts were further subjected to characterization/identification as these were also too low.

Analysis of the harvested crop samples demonstrated very little uptake of ^{14}C-residues. Of the radioactivity taken up by plants, only limited amounts of flonicamid were detected (≤ 13% TRRs). TFNG and TFNG-AM were identified at > 10% TRRs in most RACs. In addition to TFNG, other identified metabolites accounting for > 10% TRRs in wheat matrices and mature carrot root included TFNA-AM and TFNA-OH.

Conversely, in the field accumulation study, no quantifiable residues of flonicamid or its metabolites TFNG, TFNA, and TFNA-AM were detected in wheat (forage, straw and grain) and turnip (tops and roots) planted at either 30 or 60 days after the last application of flonicamid to the primary crop, cotton.

Based on the findings of the field crop rotation studies, the Meeting concluded that the uptake of quantifiable residues of flonicamid or its associated metabolites in secondary crops is unlikely.

Animal metabolism

Metabolism studies in rats reviewed by the 2015 JMPR and conducted using [^{14}C]flonicamid labelled at the 3-nicotinamide position, indicated that flonicamid was rapidly absorbed and quickly excreted. The majority of administered radioactivity was excreted in the urine and within the first 24 hours. There was no evidence of bioaccumulation following repeat doses. Distribution into the tissues was extensive with levels similar to blood concentrations; however, slightly higher concentrations were seen in the liver, kidneys, adrenals, thyroid and ovaries following single or repeat dosing and in the lungs following repeat dosing in males.

The main urinary residue was unchanged parent, followed by TFNA-AM, which was also the predominant metabolite in the faeces and bile. Other metabolites were TFNA in the faeces of low-dose animals, TFNA-AM N-oxide conjugate in the high-dose animals, TFNG-AM in the bile of high-dose animals and TFNG and TFNA-AM in the liver.

Metabolism studies were conducted in lactating goats where they were dosed orally once daily for 5 consecutive days with 3-pyridine-^{14}C-labelled flonicamid at a dose level equivalent to 10 ppm in feed. The major route of elimination of the radioactivity was via the urine which accounted for 49% of the administered dose (AD), while faeces accounted for up to 21% of the AD and milk accounted for 1% of the AD. Overall, the tissue burden was low, accounting for < 10% of the AD. The TRRs were highest in liver (1.2 mg eq/kg) followed by kidney (0.70 mg eq/kg), muscle (0.30–0.40 mg eq/kg) and fat (0.05–0.14 mg eq/kg).

Extraction of milk, using ethanol and ethanol:water recovered 97% TRRs and extraction of tissues and organs using ACN and ACN:water containing 1% acetic acid recovered greater than 42% TRRs. Flonicamid was rapidly metabolised in lactating goats, representing less than 6% TRRs in tissues and organs. TFNA-AM was the major component of the residue in organs (29% TRRs in liver, 31–41% TRRs in kidney), tissues (74% TRRs in fat, 42–50% TRRs in muscle) and milk (97% TRRs). The minor metabolites TFNA and 6-OH-TFNA-AM each accounted for ≤ 7% TRRs in liver, kidney, muscle and milk.

Leghorn laying hens were dosed orally once daily for 5 consecutive days with 3-pyridine-^{14}C-labelled flonicamid at a dose level equivalent to 10 ppm in feed. Approximately 91% of AD including 6% of AD from the gastrointestinal tract and its contents was recovered. Most of the AD (72%) was excreta-related. TRRs in egg white and egg yolk accounted for about 2.4% of AD (1.8% AD in egg white plus 0.6% AD in yolk). The tissue burden was low (< 6% of the AD) with highest concentrations of ^{14}C-residues found in kidney (1.4 mg eq/kg) followed by liver (1.2 mg eq/kg), muscle (evenly distributed between breast and thigh muscle; 1.0 mg eq/kg each), skin (0.70 mg eq/kg) and fat (0.15 mg eq/kg).

Extraction of eggs, tissues and organs with ACN and ACN:water containing 1% acetic acid recovered more than 81% TRR. Flonicamid accounted for only a very small percentage of the TRRs in eggs (2–4% TRRs), tissues (< 1% TRRs) and organs (< 0.5% TRRs). TFNA-AM was the predominant component of the residue in egg whites and egg yolks (≤ 96%TRRs), liver (93%TRRs), kidney (76%TRRs) and tissues (97%TRRs in both breast muscle and thigh muscle, 96%TRRs in skin and 95%TRRs in fat). Other metabolites identified in organs and tissues were OH-TFNA-AM and TFNG-AM, however, neither of these accounted for greater than 5% of TRR.

The Meeting concluded that, in all species investigated, the total administered radioactivity was quickly and almost completely eliminated in excreta. The metabolic profiles differed quantitatively between the species, but qualitatively there were no major differences. The routes and products of metabolism in animals were consistent across the studies resulting from the hydrolysis of the cyano function to the amide function as well as ring hydroxylation. Moreover, TFNA-AM was the major component of the residue in all tissues, organs, milk and eggs of livestock animals.

While the overall metabolism in plants, livestock and rats is similar, the metabolism of flonicamid in animals is more extensive with hydrolysis of flonicamid to the major amide metabolite TFNA-AM.

Methods of analysis

The Meeting received descriptions and validation data for analytical methods for residues of flonicamid and its relevant metabolites TFNA-AM, TFNA and TFNG in plant commodities and for flonicamid, TFNA-AM, TFNA, TFNG and OH-TFNA-AM in animal commodities. Residue analytical methods rely on LC/MS-MS. Typical limits of quantitation (LOQs) achieved for plant commodities fell in the range of 0.01–0.02 mg/kg for each analyte. The LOQs for milk and animal products (liver, kidney, muscle and eggs) were 0.01 mg/kg for each analyte. Methods were successfully subjected to independent laboratory validation.

The acid version (addition of 1% formic acid to the acetonitrile extraction solvent) of the QuEChERS multi residue LC-MS/MS method was used for flonicamid, TFNA, TFNG and TFNA-AM in plant matrices with LOQs of 0.01 mg/kg for each analyte.

The Meeting determined that suitable methods are available for the analysis of flonicamid and its relevant metabolites in plant and animal commodities.

Stability of residues in stored analytical samples

The Meeting received storage stability studies under freezer conditions at –17 °C for flonicamid and its relevant metabolites TFNA-AM, TFNA and TFNG for the duration of the storage of 18 to 23 months in a wide range of raw and processed crop matrices, including high-water, high-starch and high-oil crops. The Meeting concluded that residues of flonicamid, TFNA-AM, TFNA and TFNG are stable for at least 18 months. Freezer storage stability studies were also conducted concurrently with several of the crop field trials, demonstrating similar results.

All milk samples from the feeding studies were frozen at –20 ºC and analysed within 30 days after sampling. Therefore, storage stability data are not necessary. In contrast, all tissue samples were analysed within 12 months of collection. Freezer storage stability studies, conducted concurrently with the feeding studies, demonstrated that flonicamid, TFNA, TFNA-AM, OH-TFNA-AM and

TFNG were stable for 374 days in all tissues except fat. For fat, flonicamid and its metabolites were demonstrated to be stable for 315 days.

Definition of the residue

In primary crops, the parent compound represented the majority of the residue accounting for up to 61% TRRs in peach fruits, 91%TRRs in bell pepper fruits, 19% TRRs in potato and up to 50% TRRs in wheat forage, hay, straw, chaff and grain. Metabolites TFNA and TFNG were identified as predominant metabolites (> 10%TRRs) in all crop commodities. In the crop field trials, residues of TFNA and TFNG were measurable in all crops, the magnitude of which was crop-dependent. However, both the TFNA and TFNG were seen in the rat metabolism study and considered to be up to 10-fold less toxic than the parent flonicamid based on toxicity studies reviewed by the 2015 WHO.

In the field accumulation study no measurable residues of parent or any of its associated metabolites were observed in secondary crops.

In light of the above, the Meeting decided to define the residue for enforcement/monitoring and for risk assessment for plant commodities as parent only.

In the farm animal metabolism studies, the parent, flonicamid, was rapidly degraded in ruminants and poultry, accounting for ≤ 6% TRRs in all tissues, milk and eggs. Conversely, the metabolite TFNA-AM accounted for the majority of the radioactivity in goat tissues (29–74% TRRs) and milk (92–97%TRRs) and laying hen tissues (76–97% TRRs) and eggs (ca. 95%TRRs).

Similar findings were observed in the livestock feeding studies whereby flonicamid was present at very low levels in all animal commodities with the metabolite TFNA-AM representing the majority of the residues in tissues, milk and eggs. Therefore, TFNA-AM will be included in the residue definition for enforcement as a marker compound. Since the method of analysis is capable of analysing both flonicamid and TFNA-AM, the Meeting agreed to define the residue for enforcement/monitoring as flonicamid and TFNA-AM.

The log K_{ow} for flonicamid is 0.3. In the metabolism studies there was no evidence of the parent compound and TFNA-AM partitioning into fatty matrices (fat, milk and egg yolks) as the total residues were present at comparable concentrations in all livestock matrices. In the dairy cattle and poultry feeding studies, there was no evidence of the total residues of flonicamid and TFNA-AM sequestering into milk, eggs or fat. Therefore, the Meeting did not consider the residue fat soluble.

As TFNA-AM was the major component of the residue in all animal matrices in both the metabolism and feeding studies, the Meeting decided to define the residue for dietary risk assessment for animal commodities as parent and TFNA-AM.

Based on the above, the Meeting recommended that the residue definition for compliance with MRLs and estimation of dietary intake should be as follows:

Definition of the residue for compliance with MRL and estimation of dietary intake for plant commodities: *Flonicamid*

Definition of the residue for compliance with MRL and estimation of dietary intake for animal commodities: Flonicamid and the metabolite TFNA-AM, expressed as parent.

The residue is not fat soluble.

Results of supervised residue trials

Pome fruits

Results from supervised field trials on apples and pears conducted in the US were provided to the Meeting, including apple and pear data from Australia.

A total of 16 independent supervised trials were conducted in the US on apples (12) and pears (4). The GAP in the US for pome fruits allows three applications at a maximum rate of 0.1 kg ai/ha with a PHI of 21 days.

Flonicamid residues from 12 apple trials matching the US GAP were: 0.02, 0.04 (3), 0.05 (4), 0.06, 0.07, 0.10 and 0.11 mg/kg.

Flonicamid residues from four pear trials matching the US GAP were: 0.01 (3) and 0.02 mg/kg.

A total of seven independent supervised trials were also conducted on apples in Australia according to the Australian GAP which allows three applications at a maximum rate of 0.01 kg ai/hL with a PHI of 21 days. Nine supervised trials were conducted on pears in Australia, however, in the absence of an Australian GAP, these trials were not considered.

Flonicamid residues from seven apple trials matching the Australia GAP were 0.09, 0.12 (2), 0.13, 0.15, 0.22 and 0.24 mg/kg.

The Meeting noted that in the US a group GAP for pome fruit exists and decided to explore the possibility of setting a group maximum residue level. As the supervised trials on apples conducted in Australia in accordance with the Australian GAP lead to the higher residues, the Meeting recommended that the group maximum residue level be based on the dataset from Australia.

Based on the Australian residue data for apples, the Meeting estimated a maximum residue level for pome fruits of 0.8 mg/kg and an STMR of 0.13 mg/kg.

Stone fruits

Results from supervised field trials on peaches, cherries and plums conducted in the US were provided to the Meeting.

A total of 19 independent supervised trials were conducted in the US on peaches (8), cherries (6) and plums (5) according to the US GAP on stone fruits which allows three applications at a maximum rate of 0.1 kg ai/ha with a 14-day PHI.

Residues of flonicamid from eight peach trials matching the US GAP for stone fruits were: 0.09 (2), 0.10, 0.13, 0.15, 0.22 (2) and 0.42 mg/kg.

Residues of flonicamid from six cherry trials matching the US GAP for stone fruits were: 0.26, 0.27 (2), 0.28 (2) and 0.36 mg/kg.

Residues of flonicamid from five plum trials matching the GAP for stone fruits were: 0.01, 0.02, 0.03 and 0.04 (2) mg/kg.

The Meeting noted that in the US a group GAP for stone fruits exists and decided to explore the possibility of setting a group maximum residue level. Since median residues among the representative commodities were not within a 5-fold range (0.14 mg/kg vs. 0.28 mg/kg vs. 0.03 mg/kg), the Meeting decided to estimate maximum residue levels for each subgroup based on the individual dataset for each representative commodity.

The Meeting estimated a maximum residue level of 0.9 mg/kg and an STMR of 0.28 mg/kg for cherries subgroup.

The Meeting estimated a maximum residue level of 0.7 mg/kg and an STMR of 0.14 mg/kg for peaches subgroup.

The Meeting estimated a maximum residue level of 0.1 mg/kg and an STMR of 0.03 mg/kg for plums subgroup.

Strawberries

Results from supervised field trials on strawberries conducted in the US were provided to the Meeting.

A total of eight independent supervised trials were conducted in the US on strawberries according to the US GAP for low growing berries, which allows three applications at a maximum rate of 0.1 kg ai/ha with a 0-day PHI.

Residues of flonicamid matching the US GAP were: 0.13, 0.19, 0.27, 0.33, 0.41, 0.47, 0.54 and 0.59 mg/kg.

The Meeting estimated a maximum residue level of 1.5 mg/kg and an STMR of 0.37 mg/kg for low growing berries.

Brassica (Cole or cabbage) vegetables, Head cabbages, Flowerhead brassicas

Results from supervised field trials on cabbage and broccoli conducted in the US were provided to the Meeting.

A total of 12 independent supervised trials were conducted in the US on broccoli (6) and cabbage (6) according to the US GAP on Brassica (Cole) Leafy Vegetables which allows three applications at a maximum rate of 0.1 kg ai/ha with a 0-day PHI.

Residues of flonicamid from six broccoli trials matching the US GAP for Brassica (Cole) leafy vegetables were: 0.250, 0.428, 0.432, 0.462, 0.499 and 0.553 mg/kg.

Residues of flonicamid from six trials on cabbage (with wrapper leaves) matching the US GAP for Brassica (Cole) Leafy Vegetables were: < 0.025, 0.025, 0.062, 0.205, 0.288 and 1.262 mg/kg.

Residues of flonicamid from six trials on cabbage (without wrapper leaves) matching the US GAP for Brassica (Cole) Leafy Vegetables were: < 0.025 (6) mg/kg.

The Meeting noted that in the US a group GAP for Brassica (Cole) leafy vegetables exists and decided to explore the possibility of setting a group maximum residue level. Since median residues among the representative crops were within a 5-fold range (0.45 mg/kg vs. 0.134 mg/kg) and the Mann-Whitney test indicated that the residues were not statistically different, the Meeting decided to estimate a group maximum residue level based on the following combined residues: < 0.025(7), 0.025, 0.062, 0.205, 0.288 and 1.262 mg/kg.

The Meeting estimated a maximum residue level of 2.0 mg/kg and an STMR of 0.358 mg/kg for Brassica (Cole or cabbage) vegetables, head cabbages and flowerhead Brassicas.

The Meeting estimated an STMR of 0.02 mg/kg for cabbage (without wrapper leaves).

Fruiting vegetables, Cucurbits

Supervised field trials on field- and greenhouse-grown melons conducted in Southern EU and on field-grown pumpkins conducted in Hungary were provided to the Meeting. However, only four trials on melons and four trials on pumpkins matched the critical GAP of Slovenia which allows three foliar spray applications of a WG formulation at 0.05 kg ai/ha with a re-treatment interval of 7 days and a PHI of 1 day. Therefore, in the absence of a sufficient number of trials matching the Slovenia critical GAP, these trials were not considered further.

A total of 17 independent supervised trials, conducted in the US on cucumber (6), melon (6) and summer squash (5) according to the US GAP on cucurbit vegetables, which allows three applications at a maximum rate of 0.1 kg ai/ha with a 0-day PHI, were provided to the Meeting. In addition, the Meeting received four greenhouse cucumber trials conducted in Canada and the US according to the US critical GAP which allows two foliar spray or soil applications at a maximum rate 0.15 kg ai/ha with a re-treatment interval of 6–7 days and a 0-day PHI.

Residues of flonicamid from six field cucumber trials matching the US GAP for cucurbit vegetables were: 0.04, 0.06 (3), 0.07 and 0.12 mg/kg.

Residues of flonicamid from six melon trials matching the US GAP for cucurbit vegetables were: 0.020, 0.03, 0.04, 0.05, 0.06 and 0.09 mg/kg.

Residues of flonicamid from five summer squash trials matching the US GAP for cucurbit vegetables were: 0.01, 0.03 (3) and 0.04 mg/kg.

Residues of flonicamid from the greenhouse cucumber trials matching the US GAP for the foliar spray application were: 0.05, 0.06, 0.14 and 0.54 mg/kg.

Residues of flonicamid from the greenhouse cucumber trials where the growth media was treated were: 0.09, 0.13, 0.16 and 0.20 mg/kg.

For greenhouse cucumbers, as there is an insufficient number of supervised trials conducted in accordance with the US critical GAP, the Meeting did not consider these trials further.

In addition to the US trials, the Meeting received 10 independent supervised field trials conducted in Australia on cucumbers (2), melons (5) and summer squash (3) according to the Australian GAP on cucurbit vegetables which allows three applications at a maximum rate of 0.1 kg ai/ha with a 1-day PHI.

Residues of flonicamid from two field cucumber trials matching the Australian GAP for Cucurbit Vegetables were: 0.03 (2) mg/kg.

Residues of flonicamid from five melon trials matching the Australian GAP for Cucurbit Vegetables were: 0.03, 0.05 (2), 0.09 and 0.17 mg/kg.

Residues of flonicamid from three summer squash trials matching the Australian GAP for Cucurbit Vegetables were: 0.01, 0.04 and 0.08 mg/kg.

Since the use of flonicamid on the cucurbits crop group is registered in Australia, the residue decline trials demonstrated limited dissipation of flonicamid residues with increasing PHI and that there are an insufficient number of Australian trials at the critical GAP, the Meeting compared the US field trials against the Australian GAP and combined them as follows:

Residues of flonicamid in field cucumbers from eight trials were: 0.03 (2), 0.04, 0.06 (3), 0.07 and 0.12 mg/kg.

Residues of flonicamid in melons from 11 trials were: 0.02, 0.03(2), 0.04 (2), 0.05 (2), 0.06, 0.09 (2) and 0.17 mg/kg.

Residues of flonicamid in summer squash from eight trials were: 0.01 (2), 0.03 (3), 0.04 (2) and 0.08 mg/kg.

The median residues among the representative crops were within a 5-fold range (0.06 mg/kg vs. 0.05 vs 0.03 mg/kg) and the Kruskall-Wallis test indicated that the residues were not statistically different, therefore, the Meeting decided to combine the dataset as follows: 0.01 (2), 0.02, 0.03 (7), 0.04 (5), 0.05 (2) 0.06 (4), 0.07, 0.08, 0.09 (2), 0.12 and 0.17 mg/kg.

The Meeting estimated a maximum residue level for fruiting vegetables, cucurbits, of 0.2 mg/kg and an STMR of 0.04 mg/kg.

Fruiting vegetables, other than cucurbits

Results from supervised field trials on tomatoes, bell peppers and non-bell peppers were conducted in the US as well as supervised trials on greenhouse tomatoes conducted in Canada and the US were provided to the Meeting.

A total of 34 independent supervised trials were conducted in the US on field tomatoes (26), bell peppers (6) and non-bell peppers (2) according to the US GAP on fruiting vegetables, which allows three foliar spray applications of a WG formulation at a maximum rate of 0.1 kg ai/ha or two applications of a SG formulation at a maximum rate of 0.15 kg ai/ha. For both formulations, the crops may be harvested at a 0-day PHI.

Three additional trials were conducted in Canada and the US on greenhouse tomatoes where treatments were conducted according to the US GAP which allows two foliar spray applications at a maximum rate of 0.15 kg ai/ha with a 0-day PHI.

Only field tomato trials were conducted with both the WG and SG formulations, however, it was not clear which formulation resulted in the critical GAP:

Residues of flonicamid from 12 field tomato trials where the WG formulation was applied according to the US critical GAP for fruiting vegetables were: 0.03, 0.05, 0.06, 0.07, 0.08, 0.09 (3), 0.14, 0.15, 0.22 and 0.23 mg/kg.

Residues of flonicamid from 14 field tomato trials where the SG formulation was applied according to the US critical GAP for fruiting vegetables were: < 0.01, 0.05(2), 0.06, 0.07, 0.08, 0.10 (2), 0.11, 0.12 (2), 0.13, 0.15 and 0.19, mg/kg.

As highest residues in tomatoes were observed following treatment with the WG formulation, only these were considered when estimating the maximum residue level.

Residues of flonicamid from six bell pepper trials matching the US critical GAP for fruiting vegetables were: 0.06 (3), 0.10 and 0.11 (2) mg/kg.

Residues of flonicamid from two non-bell pepper trials matching the US critical GAP for fruiting vegetables, other than cucurbits were: 0.21 and 0.22 mg/kg.

As the GAP in the US is for the fruiting vegetables crop group, the median values from the trials conducted in the US on tomatoes, bell peppers and non-bell peppers were within 5-fold (0.09 mg/kg vs 0.08 mg/kg vs 0.21 mg/kg) and the Kruskall-Wallis test indicated that the residues from field trials were not statistically different, the Meeting decided to estimate a group maximum residue level. The residues in tomatoes, bell peppers and non-bell peppers were combined as follows: 0.03, 0.05, 0.06 (4), 0.07, 0.08, 0.09 (3), 0.10, 0.11 (2), 0.14, 0.15, 0.21, 0.22 (2) and 0.23 mg/kg.

The Meeting estimated a maximum residue level of 0.4 mg/kg and an STMR of 0.09 mg/kg for fruiting vegetables, other than cucurbits, excluding mushrooms and sweet corn.

Leafy vegetables

Leafy vegetables (excluding Brassica leafy vegetables)

Results from supervised field trials on head lettuce, leaf lettuce, spinach and radish leaves conducted in the US were provided to the Meeting.

A total of 18 independent supervised trials were conducted in the US on head lettuce (6), leaf lettuce (6) and spinach (6) according to the US GAP on leafy vegetables which allows three applications at a maximum rate of 0.1 kg ai/ha with a 0-day PHI.

A total of five independent supervised trials were conducted in the US on radish leaves according to the US GAP on root and tuber vegetables which allows three applications at a maximum rate of 0.1 kg ai/ha with a 3-day PHI.

Residues of flonicamid from six head lettuce (with wrapper leaves) trials matching the US GAP for leafy vegetables were: 0.39, 0.43, 0.49, 0.52, 0.58 and 0.62 mg/kg.

Residues of flonicamid from six trials on leaf lettuce matching the US GAP for leafy vegetables (except Brassica) were: 1.94, 2.18, 2.52, 2.67, 2.71, 3.06 and 3.11 mg/kg.

Side-by-side trials were conducted on cos lettuce comparing the WG formulation with the SG formulation with and without surfactant. These trials were not considered further in the estimation of the maximum residue level.

Residues of flonicamid from six trials on spinach matching the US GAP for leafy vegetables were: 4.82, 4.86, 5.71, 5.73, 6.59 and 6.97 mg/kg.

Residues of flonicamid from five trials on radish leaves matching the US GAP for root and tuber vegetables were: 0.21, 3.1, 5.4, 5.7 and 8.5 mg/kg.

As the GAP in the US is established for the leafy vegetables crop group, the Meeting decided to explore the possibility of setting a group MRL. The median residues in head lettuce, leaf lettuce and spinach, which are the representative commodities for this subgroup, differed by more than 5-fold (0.51 mg/kg vs 2.67 mg/kg vs 5.72 mg/kg). In addition, as the GAP for radish leaves differs from that

of the other leafy vegetables, the Meeting decided to estimate maximum residue levels for each commodity based on the individual datasets without extrapolation to the entire subgroup.

The Meeting estimated a maximum residue level of 1.5 mg/kg and an STMR of 0.51 mg/kg for head lettuce with wrapper leaves.

For leaf lettuce, the Meeting estimated a maximum residue level of 8 mg/kg and an STMR of 2.67 mg/kg

The Meeting estimated a maximum residue level of 20 mg/kg and an STMR of 5.72 mg/kg for spinach.

The Meeting estimated a maximum residue level of 20 mg/kg and an STMR of 8.50 mg/kg for radish leaves.

Brassica leafy vegetables

Results from supervised field trials on mustard greens conducted in the US were provided to the Meeting.

A total of eight independent supervised trials were conducted in the US on mustard greens according to the US GAP on Brassica (Cole) leafy vegetables which allows three applications at a maximum rate of 0.1 kg ai/ha with a 0-day PHI.

Residues of flonicamid from eight trials on mustard greens matching the US GAP for Brassica (Cole) leafy vegetables were: 2.04, 2.21, 3.96, 4.40, 4.78, 4.92, 6.87 and 8.31 mg/kg.

The Meeting estimated a maximum residue level of 15 mg/kg and an STMR of 8.31 mg/kg for the Brassica leafy vegetables subgroup.

Root and tuber vegetables

Results from supervised field trials on potatoes, carrots and radish roots conducted in the US and Australia (potatoes only) were provided to the Meeting.

A total of 23 independent supervised trials were conducted in the US on potatoes (16), carrots (2) and radishes (5) according to the critical GAP in the US which allows three applications at a maximum rate of 0.1 kg ai/ha with a 7-day PHI for potatoes and a 3-day PHI for carrots and radishes.

Residues of flonicamid from 16 potato trials matching the US GAP were: < 0.01 (15) and 0.015 mg/kg.

Residues of flonicamid from two carrot trials matching the US GAP were: 0.02 (2) mg/kg.

Residues of flonicamid from five radish trials matching the US GAP were: 0.02, 0.07, 0.10, 0.13 and 0.21 mg/kg.

The Meeting noted that in the US, group GAPs for root and tuber vegetables and tuberous and corm vegetables exist; however, as these GAPs are different for each crop group and there is an insufficient number of supervised residue trials provided for carrots, the Meeting decided to estimate individual maximum residue levels for potato and radish roots only.

For potatoes, the Meeting estimated a maximum residue level of 0.015 mg/kg and an STMR of 0.01 mg/kg.

The Meeting estimated a maximum residue level of 0.4 mg/kg and an STMR of 0.10 mg/kg for radish roots.

Celery

Results from supervised field trials on celery conducted in the US were provided to the Meeting.

A total of six independent supervised trials were conducted in the US on celery according to the US GAP for leafy vegetables, except Brassica vegetables, which includes the leaf petioles subgroup, and allows three applications at a maximum rate of 0.1 kg ai/ha with a 0 PHI.

Residues of flonicamid matching the US GAP were: 0.35, 0.43, 0.44, 0.45, 0.46, 0.93 mg/kg.

The Meeting estimated a maximum residue level of 1.5 mg/kg and an STMR of 0.45 mg/kg for celery.

Cereal grains

Results from supervised trials on wheat and barley conducted in Northern and Southern EU were provided to the meeting.

A total of 23 independent supervised trials were conducted in EU on wheat (15) and barley (8). The wheat trials were conducted according to the Slovenia GAP which allows two applications at a maximum rate of 0.07 kg ai/ha with a 28-day PHI.

As there is no GAP for barley, these trials were not considered further.

Residues of flonicamid in wheat grain matching the Slovenia GAP were: < 0.01 (11), 0.01, 0.02, 0.04 and 0.06 mg/kg.

The Meeting estimated a maximum residue level of 0.08 mg/kg and an STMR of 0.01 mg/kg for wheat.

Tree nuts

Results from supervised field trials on almonds, pecans and pistachios conducted in the US were provided to the Meeting.

A total of 12 independent supervised trials were conducted in the US on almonds (5), pecans (5) and pistachios (2) according to the US GAP which allows three applications at a maximum rate of 0.1 kg ai/ha with a 40-day PHI.

Residues of flonicamid in almond nutmeats matching the US GAP were: < 0.01 (5) mg/kg.

Residues of flonicamid in pecan nutmeats matching the US GAP were: < 0.01 (5) mg/kg.

Residues of flonicamid in pistachios matching the US GAP were 0.02 and 0.04 mg/kg.

As the Meeting could not conclude that there are no measurable residues in all tree nuts in the tree nut crop group and considering the insufficient number of supervised residue trials for pistachios, the Meeting agreed to estimate individual maximum residue levels for almonds and pecans at 0.01* mg/kg with an STMR of 0.01 mg/kg.

Oilseeds

Rape seed

Results from supervised field trials on rape seed conducted in the US were provided to the Meeting.

A total of nine independent supervised trials were conducted in the US on rape seed according to the US GAP which allows three applications at a maximum rate of 0.1 kg ai/ha with a 7-day PHI.

Residues of flonicamid matching the US GAP were: < 0.02, 0.02 (3), 0.04, 0.08, 0.09, 0.17 and 0.33 mg/kg.

The Meeting estimated a maximum residue level of 0.5 mg/kg and an STMR of 0.04 mg/kg for rape seed.

Cotton seed

Results from supervised field trials on cotton conducted in the US and Australia were provided to the Meeting.

The GAP in the US is three applications at a maximum rate of 0.1 kg ai/ha with a 30-day PHI while the GAP in Australia is three applications at a maximum rate of 0.07 kg ai/ha with a 7-day PHI.

As the critical GAP is in Australia, only the Australian trials were considered.

Residues of flonicamid in cottonseed from eight independent supervised residue trials matching the Australian critical GAP were: 0.01 (2), 0.02, 0.04, 0.09, 0.13, 0.16 and 0.34 mg/kg.

The Meeting estimated a maximum residue level of 0.6 mg/kg and an STMR of 0.06 mg/kg for cottonseed.

Mint

Results from supervised field trials on fresh mint leaves conducted in the US were provided to the Meeting.

A total of three independent supervised trials were conducted in the US on mint according to the US GAP which allows three applications at a maximum rate of 0.1 kg ai/ha with a 7-day PHI.

Residues of flonicamid matching the US GAP were: 1.70, 1.92 and 2.36 mg/kg.

The Meeting estimated a maximum residue level of 6 mg/kg and an STMR of 1.92 mg/kg for mint.

Dried hops

Results from supervised field trials on dried hops conducted in the US were provided to the Meeting.

A total of four independent supervised trials were conducted in the US on dried hops according to the US GAP which allows three applications at a maximum rate of 0.1 kg ai/ha with a 10-day PHI.

Residues of flonicamid matching the US GAP were: 0.56, 1.15, 2.82 and 9.33 mg/kg.

The Meeting estimated a maximum residue level of 20 mg/kg and an STMR of 1.98 mg/kg for dried hops.

Teas

Results from supervised field trials on tea conducted in Japan were provided to the Meeting.

A total of two independent supervised trials were conducted in Japan on tea according to the Japanese GAP which allows one application at a maximum rate of 0.1 kg ai/ha with a 7-day PHI.

Residues of flonicamid in green tea leaves matching the Japanese GAP were: 15.7 and 20.1 mg/kg.

There is insufficient data for the Meeting to estimate a maximum residue level.

Animal feeds

Straw, fodder and forage of cereal grains and grasses including buckwheat fodder forage

Wheat

Results from supervised trials on wheat and barley conducted in Northern and Southern EU were provided to the meeting.

A total of 23 independent supervised trials were conducted in EU on wheat (15) and barley (8). The wheat trials were conducted according to the Slovenia GAP which allows two applications at a maximum rate of 0.07 kg ai/ha with a 28-day PHI.

As there is no GAP for barley, these trials were not considered further.

Residues of flonicamid in wheat forage matching the Slovenia Gap were: 0.64, 0.69, 0.83, 0.88 and 0.99 (2).

The Meeting estimated a maximum residue level of 3.0 mg/kg and a median of 0.86 mg/kg for wheat forage.

Residues of flonicamid in wheat straw matching the Slovenia GAP were: < 0.02 (5), 0.02, 0.04 (2), 0.05 (3), 0.08, 0.09, 0.11 and 0.23 mg/kg.

The Meeting estimated a maximum residue level of 0.3 mg/kg and a median of 0.04 mg/kg for wheat straw and fodder, dry.

Alfalfa

Results from six independent supervised field trials on alfalfa (4) and clover (2) conducted in the US were provided to the Meeting.

The US GAP for alfalfa grown west of the Rockies allows two applications at a maximum rate of 0.10 kg ai/ha with PHIs of 14 days for seed and forage and 60 days for hay.

Two supervised trials were conducted on clover in the US, however, in the absence of a US GAP, these trials were not considered.

Four trials were conducted on alfalfa in the US, of which only two were conducted according to the US GAP. In the absence of a sufficient number of trials, the Meeting could not estimate a maximum residue level or a median residue for alfalfa seed, forage and hay.

Miscellaneous fodder and forage crops (fodder)

Almond hulls

Results from supervised field trials on almonds conducted in the US were provided to the Meeting.

Five independent trials were conducted on almonds in the US. The GAP in the US allows three applications at a maximum rate of 0.10 kg ai/ha with a PHI of 40 days.

Residues in almond hulls (dry weight) from five trials matching US GAP were: 0.92, 1.09, 1.81, 2.75 and 4.73 mg/kg. The meeting estimated a maximum residue level of 9 mg/kg and a median residue of 1.8 mg/kg.

Cotton gin trash

Results from supervised field trials on cotton conducted in the US and Australia were provided to the Meeting.

The GAP in the US is three applications at a maximum rate of 0.1 kg ai/ha with a 30-day PHI while the GAP in Australia is three applications at a maximum rate of 0.07 kg ai/ha with a 7-day PHI.

As the critical GAP is in Australia, only the Australian trials were considered.

The residues of flonicamid in cotton gin trash from eight independent supervised trials matching the Australian critical GAP were: 0.66, 1.20, 1.33, 1.60, 1.70, 2.30, 2.75, 3.00 and 3.72 mg/kg.

The Meeting estimated a median residue of 1.7 mg/kg.

Fate of residues during processing

High temperature hydrolysis

To simulate the degradation of flonicamid during pasteurization, baking, brewing, boiling and sterilisation, the hydrolysis of radio-labelled flonicamid was investigated in sterile buffered aqueous solutions.

After incubation at 90 °C (pH 4) for 20 minutes, 100 °C (pH 5) for 60 minutes or 120 °C (pH 6) for 20 minutes, no loss of radioactivity occurred. More specifically, flonicamid accounted for at least 96% of the applied radioactivity. Therefore, very limited degradation of flonicamid was observed

in aqueous buffer solutions under all the conditions tested with no significant degradation product being formed.

Processing

The Meeting received information on the fate of flonicamid residues and its metabolites TFNA-AM, TFNA and TFNG during the processing of raw agricultural commodities (RAC) like apples, peaches, plums, tomatoes, potatoes, rape seed, cotton and mint.

Processing factors calculated for the processed commodities of the above raw agricultural commodities are shown in the table below. STMR-Ps were calculated for processed commodities for which maximum residue levels were estimated.

RAC	Processed Commodity	Calculated processing factors	Best estimate	STMR-P
		Flonicamid		
Peaches	Canned peaches	0.3, 0.5, 0.3, 3.3	0.3 (median)	0.08
	Juice	1.0, 1.0, 0.3, 0.5	0.8 (median)	1.8
	Jam	0.3, 1.0, 1.0, 0.2	0.7 (median)	0.16
	Puree	0.7, 1.0, 1.0, 0.8	0.9 (median)	0.21
Plums	Dried prunes	1.0	1.0	0.04
Tomato	Paste	16.1	16.1	1.45
Potato	Chips	0.95	0.95	0.01
	Flakes	2.7	2.7	0.03
Canola	Refined oil	< 0.1	0.1	0.004
Cotton	Refined oil	< 0.24 (US), 0.6 and 0.04 (AUS)	0.32 (mean; AUS)	0.02
Mint	Oil	< 0.03	0.03	0.06

As the residue concentration in both apple juice and apple pomace were higher than in fresh apple which is not physically possible, the Meeting determined that the apple processing study was not reliable and did not calculate a processing factor for juice.

As the residue concentration is higher in tomato paste than in fresh tomato, the Meeting estimated a maximum residue level of 7.0 mg/kg by multiplying the maximum residue level for fruiting vegetables, other than cucurbits, (0.4 mg/kg) by 16.1.

Residues in animal commodities

Farm animal feeding studies

The Meeting received information on the residue levels arising in tissues and milk when three groups of dairy cows were fed with a diet containing 2.50, 6.89 and 23.7 ppm of a 1:1 mixture of flonicamid:TFNG for 28 consecutive days. As demonstrated in the metabolism studies, residues of TFNG present in feed items may be converted to TFNA-AM. Therefore, the Meeting concluded that the test material used in the feeding studies was appropriate.

In milk, no quantifiable (< LOQ) residues of flonicamid were detected in any test group. For TFNA-AM, the average residues increased from < LOQ in the low dose group to 0.02 mg/kg in the mid dose group and to 0.08 mg/kg in the high dose group.

In liver, no quantifiable residues of flonicamid were detected. For TFNA-AM, residues were detected in the mid and high dose groups above the LOQ using two different analytical methods (FMC-P-3580/RCC 844743) with different LOQ (0.025/0.01 mg/kg). TFNA-AM levels increased from less than LOQ in the low dose group to 0.039/0.02 mg/kg in the mid dose group and 0.113/0.05 mg/kg in the high dose group.

In kidney, TFNA-AM was detected in the medium and high dose groups above the LOQ using the same analytical methods as those used for kidney. TFNA-AM levels increased from levels below

LOQ in the low dose group to 0.031/0.02 mg/kg in the mid dose group and 0.105/0.09 mg/kg in the high dose group.

In muscle, only TFNA-AM was found. The level increased from below LOQ (0.025 mg/kg) in the low dose group to 0.027 mg/kg in the mid dose group and 0.088 mg/kg in the high dose group. Similarly, only TFNA-AM was measurable in fat and only at the high dose level (0.015 mg/kg).

The Meeting also received information on the residue levels arising in tissues and eggs when groups of laying hens were fed with a diet containing 0.26, 2.51, 7.47 and 25.83 ppm of a 1:1 mixture of flonicamid:TFNG for 28 consecutive days.

The average flonicamid residues in eggs increased from < LOQ in the very low and low dose groups to 0.02 mg/kg in the mid dose group and to 0.08 mg/kg in the high dose group. Average residues of TFNA-AM increased from < LOQ in the very low and low dose groups to 0.27 mg/kg in the mid dose group and 0.95 mg/kg in the high dose group.

No quantifiable residues (< LOQ) of flonicamid were found in muscle in any treatment group. No quantifiable residues (< LOQ) of TFNA-AM was measurable in muscle at the very low dose group, but there appeared to be a dose response relationship at all other dose levels; 0.049 mg/kg in the low dose group, 0.168 mg/kg in the mid dose group and 0.654 mg/kg in the high dose group.

In liver and fat, no quantifiable residues (< LOQ) of flonicamid were found at any dosing level. For liver, TFNA-AM residues increased from < 0.01 mg/kg (very low) to 0.05 mg/kg (low) to 0.17 mg/kg (mid) and 0.71 mg/kg (high) while for fat, TFNA-AM residues increased from 0.01 mg/kg (very low) to 0.02 mg/kg (low) to 0.06 mg/kg (mid) and 0.29 mg/kg (high).

Estimated dietary burdens of farm animals

Maximum and mean dietary burden calculations for flonicamid are based on the feed items evaluated for cattle and poultry as presented in Annex 6. The calculations were made according to the livestock diets from Australia, the EU, Japan and US-Canada in the OECD feeding table.

The foliar application of flonicamid to apples, cabbage, potato, almonds, rape seed, cotton and wheat resulted in residues of flonicamid in the following feed items: wet apple pomace, head cabbage with wrapper leaves, potato culls, almond hulls, rape seed meal, undelinted cottonseed, cotton seed hulls, cottonseed meal, gin trash, wheat forage, grain and straw. Based on the named feed items, the calculated maximum animal dietary burden for dairy or beef cattle was in Australia (3.96 ppm), followed by EU (1.39 ppm) and US-Canada (0.29 ppm).

	Livestock dietary burden, flonicamid, ppm of dry matter							
	US-Canada		EU		Australia		Japan	
	Max	Mean	Max	Mean	Max	Mean	Max	Mean
Beef cattle	0.27	0.13	1.39	1.02	3.96 a	3.44 c	0.003	0.003
Dairy cattle	0.81	0.70	0.82	0.71	2.38 b	2.07 d	0.002	0.002
Poultry—broiler	0.03	0.03	0.01	0.01	0.02	0.02	0	0
Poultry—layer	0	0	0.40 e	0.34 f	0	0	0	0

[a] Suitable for MRL estimates for mammalian meat, fat and edible offal

[b]. Suitable for MRL estimates for milk

[c] Suitable for STMR estimates for mammalian meat, edible offal

[d] Suitable for STMR estimate for milk

[e] Suitable for MRL estimates for eggs, meat, fat and edible offal of poultry

[f] Suitable for STMR estimates for eggs, meat, fat and edible offal of poultry

Animal commodities maximum residue level estimation

As all dietary burdens were lower than the lowest feeding levels from the dairy cow and laying hen feeding studies and since all residues of flonicamid and TFNA-AM were below the limit of

quantitation at the lowest feeding levels, there is no expectation of any measurable transfer of residues from the feed items into the livestock commodities (see tables below).

	Feed level (ppm) for milk residues	Total flonicamid and TFNA-AM residues in milk (mg/kg)	Feed level for tissue residues (ppm)	Flonicamid and TFNA-AM Residues			
				Muscle	Liver	Kidney	Fat
Maximum residue level—beef or dairy cattle							
Feeding study	2.50	0.043	2.50 6.89	< 0.045 0.050	< 0.045 0.062	< 0.045 0.054	< 0.02 < 0.02
Dietary burden and residue estimate	2.38	0.04	3.96	0.047	0.051	0.048	< 0.02
STMR—beef or dairy cattle							
Feeding study	2.50	0.041	2.50 6.89	< 0.045 0.047	< 0.045 0.059	< 0.045 0.051	< 0.02 < 0.02
Dietary burden and residue estimate	2.07	0.04	3.44	0.045	0.048	0.046	< 0.02

	Feed level (ppm) for egg residues	Total flonicamid and TFNA-AM residues in eggs (mg/kg)	Feed level for tissue residues (ppm)	Flonicamid and TFNA-AM Residues		
				Muscle	Liver	Fat
Maximum residue level—poultry broiler or layer						
Feeding study	0.26 2.51	0.02 0.11	0.26 2.51	< 0.02 0.07	< 0.02 0.08	< 0.02 0.04
Dietary burden and residue estimate	0.40	0.03	0.40	0.02	0.02	0.02
STMR—poultry broiler or layer						
Feeding study	0.26 2.51	0.02 0.09	0.26 2.51	< 0.02 0.06	< 0.02 0.06	< 0.02 0.03
Dietary burden and residue estimate	0.34	0.02	0.34	0.02	0.02	0.02

The Meeting estimated maximum residue levels of 0.02* mg/kg for mammalian fats, 0.04 mg/kg for milks and 0.05 mg/kg for meat from mammals other than marine mammals and 0.06 mg/kg for edible offal (mammalian). The STMRs for mammalian fats, milks, meat from mammals other than marine mammals and edible offal (mammalian) are 0.02 mg/kg, 0.04 mg/kg. 0.047 mg/kg and 0.051 mg/kg, respectively.

In addition, the Meeting estimated maximum residue levels of 0.02* mg/kg for poultry meat (including Pigeon meat), poultry fats and edible offal of poultry and 0.03 mg/kg for eggs. The STMRs were 0.02 mg/kg, 0.02 mg/kg, 0.02 mg/kg and 0.02 mg/kg for meat, edible offal, fat and eggs, respectively.

RECOMMENDATIONS

On the basis of the data from supervised trials the Meeting concluded that the residue levels listed in Annex 1 are suitable for establishing maximum residue limits and for IEDI assessment.

Definition of the residue for compliance with the MRL and for estimation of dietary intake for plant commodities: *Flonicamid*